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DRUG DISCOVERY

Studies on the anticonvulsant and sedative effects of *Jatropha curcas* (Euphorbiaceae) and *Phragmanthera capitata (*Loranthaceae) in mice

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ABSTRACT

The species of *Jatropha curcas* and *Phragmanthera capitata* are used in the treatment of various ailments in African traditional medicine such as insomnia and convulsive disorders. This study was, therefore, performed to scientifically ascertain their anticonvulsant and sedative effects using animal models. Pentylenetetrazol (PTZ) and isoniazid (INH)-induced seizure models, and phenobarbital-induced sleeping-time model were used. *Jatropha curcas* root extract (JCE) and *Phragmanthera capitata* ariel extract (PCE) were obtained by cold maceration. Acute toxicity (LD_{50}) tests, as well as phytochemical screening, were determined using standard methods. PCE (200, 400, 800 mg/kg) dose-dependently exhibited significant ($P<0.01$) delay in latency of clonic-tonic convulsions with percentage protection of 20, 40 and 60 %, respectively. JCE (200, 400, 800 mg/kg) showed significant reductions in latency of tonic-clonic convulsions with zero protection against PTZ lethality. In INH-model, PCE (800 mg/kg) significantly ($P<0.01$) delayed the onset of INH-induced tonic-clonic seizures with zero protection. JCE (at 400 and 800 mg/kg) caused 20 and 40 % protection respectively compared to 80 % in diazepam-treated group. Both extracts at the different doses (200, 400, 800 mg/kg) dose-dependently exhibited significant reduction in onset of sleep (sleep latency) and potentiate the duration of sleep with values 227.4±2.04, 239.2±9.15, 283.2±1.62 and 226.9±5.89, 233.2±2.32, 287.6±5.48 minutes, respectively, relative with the control (213.2±4.12). The phytochemical analysis revealed the presence of flavonoids, tannins, alkaloids, phlobatanins and saponins. The LD_{50} for both extracts was greater than 3000 mg/kg. The results showed that the extracts of *J. curcas* and *P. capitata* exhibited anticonvulsant and sedative activities in support of their folkloric use.

Keywords: *Jatropha curcas, Phragmanthera capitata,* Pentylenetetrazole (PTZ) Isoniazid (INH), Phenobarbital (PB).

1. INTRODUCTION

The therapeutic use of medicinal plants dates back to many centuries. Historically, it is well known that 80 per cent of chemical entities introduced as drugs worldwide were of natural origins or derived from natural products. In Africa, there are several thousands of plants being used commonly to treat various ailments (Okigbo and Mmmeka, 2006), but only a small fraction has scientifically being investigated for their bioactivity. In recent times, continuous investigation of medicinal plants in an attempt to discover new "drug leads" for prevention and cure of various pathologies has occupied the mainstream of academic researches worldwide.

The species of *Jatropha curcas* and *Phragmanthera capitata* are used traditionally to cure various human diseases in Africa, Latin America, India and South-East Asia (Fairless, 2007; Adesina *et al.,* 2013), with claims of high efficacy. *Jatropha curcas* is a multipurpose, drought-resistant perennial plant belonging to the Euphorbiaceae family. It is cultivated abundantly in many tropical and sub-tropical regions of the world. It has thick glabrous branches, straight trunk and grey or reddish bark, masked by large white patches (Abubakar *et al.,* 2016). It is used for the treatment of dermatomucosal diseases, gonorrhoea, arthritis, gout, jaundice, toothache, gum inflammation, gum bleeding, diarrhoea and pyorrhea, and several other disease states (Okoli *et al.,* 2008; Awe *et al.,* 2010). Pharmacologically, different plant parts of *J. curcas* is documented to have analgesic (Omeh and Ezeja, 2010), antidiabetic (Igoli *et al.,* 2005), antidiarrhoeal (Sachdeva *et al.,* 2012), wound healing (Shetty *et al.,* 2006), anti-inflammatory (Salim *et al.,* 2018), antimicrobial (Onyama *et al.,* 2016) antioxidant and anticancer (Oskoueian *et al.,* 2011; Abubakar *et al.,* 2016) activities. *Phragmanthera capitata,* belonging to the Loranthaceae family, is an obligate hemiparasitic mistletoe that is abundant across the African continent (Engone and Sallé, 2006; Dibong *et al.,* 2009). Traditionally, in Cameroon folkloric medicine, *P.capitata* is used mainly for chlamydia infection, dysentery, hypertension, cancer, epilepsy, arthritis, gynaecological problems and diabetes etc. (Jayakumar, 2010; Din *et al.,* 2011). Pharmacologically, the anti-diarrheagenic (Takem *et al.,* 2014); anti-secretory, gastroprotective and anti-ulcer (Takem *et al.,* 2014); antipyretic and analgesic (Takem *et al.,* 2014); steroidogenetic and spermatogenetic (Takem, 2014); antibacterial and antifungal (Ohikhena *et al.,* 2017); anxiety-lowering (Takem *et al.,* 2014) haematopoietic (Takem *et al.,* 2015) anti-inflammatory and antioxidant (Etame Loe *et al.,* 2018) properties are well documented. Considering several studies carried out on these plants, no information regarding the anticonvulsant and sedative activities on the central nervous system (CNS) have been reported. Therefore, the present investigation was undertaken to ascertain the veracity of their folkloric usage as a treatment for convulsive disorders.

2. MATERIALS AND METHODS

Drugs and Chemicals

Pentylenetetrazole (Sigma, USA); isoniazid (Sigma Chemicals, USA); phenobarbitone (STEROP-Belgium); diazepam (JUHEL, Nigeria Limited); methanol (BDH Ltd, England), All other chemicals used in the experiments were purchased locally and were of analytical grade.

Plant Collection and Authentication

Jatropha curcas and *Phragmanthera capitata* were collected from different geographical sites of Africa during the winter season. Fresh roots of *Jatropha curcas* were collected from Orba in Udenu Local Government Area in Enugu State, Nigeria. The plant sample was identified and authenticated by Mr Alfred Ozioko of the International Centre for Ethnomedicine and Drug Development (InterCEDD), Nigeria, where a voucher specimen with the No: Inter CEDD/086 was deposited. *Phragmanthera capitata* plant was harvested from avocado trees in Konka, Baligham village in the North-Western Region of Cameroon. Authentication of the plant was by Cameroon National Herbarium (CNH) with Voucher No: 24673/SRF/CAM.

Preparation of Extract

The collected plants were cleaned and air-dried at 25 ± 2 ^{0}Cfor fifteen days and then pulverized to a fine powder. The dried powder of each plant was extracted with methanol by cold maceration with occasional stirring for 48 h. The extract was then filtered using a Buchner funnel and a sterilized cotton filter. The solvent was subjected to rotary evaporation to obtain *Jatropha curcas* extract (JCE) and *Phragmanthera capitata* extract (PCE), respectively. The crude extracts were then stored in an airtight container prior to analysis.

Animals

Albino mice (24–38 g) of either sex used for the study were obtained from the animal house facility of the Department of Pharmacology and Toxicology, University of Nigeria, Nsukka, Nigeria. They were maintained under standard laboratory conditions (12:12 h light-dark cycle, frequent air change) and had free access to water and standard animal feed *ad libitum*. The animals were acclimatized for at least 1 week before being used for experiments. All procedures were in compliance with the NIH Guidelines for Care and Use of Laboratory Animals (Pub No. 85-23, revised 1985), and in accordance with the University Ethics Committee on the Use of Laboratory Animals.

Phytochemical Screening

The methanol extracts were qualitatively screened for the presence of various phytochemical constituents such as alkaloids, reducing sugars, saponins, tannins, phlobatannins, flavonoids, steroids and starch according to standard procedures (Sofowora, 1993; Trease and Evans, 2002).

Acute Toxicity (LD_{50}) Test

The oral median lethal doses (LD_{50}) of the extracts (JCE and PCE) were evaluated as described by Lorke (1983). Briefly, in the first phase, 9 mice were randomly divided into three groups (n=3) and were orally administered with each extract at different doses (10, 100, and 1000 mg/kg), respectively. The animals were observed for 24 hours for signs of toxicity and mortality. In the second phase, 4 mice were used. Three of the mice were administered orally with each extract at doses of 1600, 2900 and 5000 mg/kg body weight, while the fourth mouse served as control (10 mL/kg). Animals were observed for another 24 h. The LD_{50} value was determined by calculating the geometric mean of the lowest lethal dose and the highest non-lethal dose.

Pentylene tetrazole induced convulsions

Adult Albino mice were divided into 5 groups (n=5). Group 1 (PTZ-induced seizure control) received the vehicle (10 ml/kg, 20% tween 80); groups 2, 3 and 4 were administered *Jatropha curcas* and *Phragmanthera capitata* extracts at doses of 200, 400 and 800 mg/kg, BW, respectively, while group 5 received diazepam (3 mg/kg, *i.p.*). Thirty minutes later, convulsions were induced by the administration of pentylene tetrazole (PTZ) (90 mg/kg, i.p). The animals were observed for the occurrence of seizures and mortality over a 60 minutes time period. Percentage of protection was also recorded in each group. Animals devoid of seizures without subsequent death during the 60 minutes observation period were considered protected (Okoye *et al.,* 2010).

Isoniazid Induced Convulsions

Isoniazid (INH) induced convulsion test was performed as per Gerhard *et al.* (2002). Adult albino mice were randomly divided into 5 groups (n=5). The dosage of extract/standard drug/animal groupings was as described above. Thirty minutes after the isoniazid

(INH, 300 mg/kg, *p.o*) administration, the animals were observed for the time of onset of tonic-clonic seizures and mortality. Percentage of protection was also recorded in each group. Animals devoid of seizures without subsequent death during the 120 minutes observation period were considered protected.

Phenobarbital (PB) Induced Sleep Test

The sedative effect was assessed as described by Rabbani *et al.* (2008), with slight modifications. Mice were randomly divided into five (5) groups of five animals each. The control (group 1) received the vehicle (10 ml/kg, 20% tween 80) while the test groups (groups 2, 3, 4 and 5) received different doses (200, 400, 800 mg/kg, *p.o*) of the extracts and diazepam (3.0 mg/kg, *i.p*). Thirty minutes after administration, phenobarbitone sodium (50 mg/kg, *i.p*) was administered to all the groups. Each animal was observed for the onset (latency) and the duration of sleep using the time between the loss and recovery of the righting reflexes.

Statistical Analysis

The values obtained were presented as mean ± standard deviation (SD) and analysed statistically using ANOVA (One-Way Analysis of Variance) followed by a post-hoc Dunnett's multiple comparison tests. Differences between mean values were considered significant at 0.1%, 1% and 5% level of significance (i.e. $P<0.001$, $P<0.01$, $P<0.05$).

3. RESULTS AND DISCUSSION

The anticonvulsant and sedative efficacy of *Jatropha curcas* and *Phragmanthera capitata* was evaluated using pentylenetetrazole (PTZ) and strychnine nitrate (STN) – induced seizure models, and phenobarbital-induced sleep model.

As shown in Table 2, a clonic spasm and tonic-clonic convulsion were observed in all the animals following PTZ (90 mg/kg, i.p) administration. Oral treatment with both extracts of *Jatropha curcas* and *Phragmanthera capitata* showed anticonvulsant activity to varying degrees in this study. PCE (at 200, 400, 800 mg/kg) dose-dependently exhibited remarkable ($P<0.01$) delay in latency to clonic-tonic convulsions with protection of 20, 40 and 60 %, respectively. JCE (at 200, 400, 800 mg/kg) demonstrated significant ($P< 0.05$, $P< 0.01$, $P<0.001$) reductions in latency to tonic convulsions with zero protection against PTZ lethality. Diazepam (3 mg/kg) employed as the standard agent, exhibited the highest degree of delay in latency to clonic and tonic convulsions (60.00±0.0) with 100% protection.

The obtained result in the INH-seizure model as summarized in Table 3 showed an elicited tonic-clonic convulsion in all the animals administered INH (300 mg/kg, p.o) with 28.80±1.68 min in control. PCE (at 800 mg/kg) significantly ($P<0.01$) delayed the onset of INH-induced tonic-clonic seizures with zero protection. At the 200 and 400 mg/kg doses, both JCE and PCE showed no significant ($P>0.05$) effect on the onset of convulsion compared with the control. However, JCE (at 400 and 800 mg/kg) caused 20 and 40 % protection; although with less activity than diazepam (3 mg/kg *i.p.*) with 100% protection against INH lethality. All the animals in the vehicle control and PCE treated groups died after seizure.

The sedative efficacy of *J. curcas* and *P. capitata* against phenobarbital-induced sleep test as described in Table 4 showed that JCE (at 200, 400, 800 mg/kg) and PCE (at 400 and 800 mg/kg), dose-dependently exhibited significant ($P< 0.01$, $P< 0.01$, $P<0.001$) reduction in onset of sleep time (sleep latency) and potentiates the duration of sleep with values 227.4±2.04, 239.2±9.15, 283.2±1.62 and 226.9±5.89, 233.2±2.32, 287.6±5.48 minutes, respectively, relative with the control (213.2±4.12). The ability to potentiate the time of sleep suggests that *J. curcas* and *P. capitata* are endowed with CNS depressant activity (Raquibul Hasan *et al.,* 2009; Okon and Davies, 2014). Similarly, diazepam (at 3.0 mg/kg) exhibited the highest efficacy in sleep latency (8.880±0.59; $P<0.001$) and duration of sleep time (302. 1 ±4.83; $P<0.001$) relative with the control (36.96±2.34, 213.4±4.12), respectively.

The above results indicate that both extracts demonstrated different levels of dose-dependent activity against PTZ and INH induced-convulsions. PCE at 800 mg/kg exhibited the highest percentage protection of 60% against PTZ-induced seizures whereas JCE at 800 mg/kg showed the highest percentage protection of 40% against INH-induced seizures. However, in consideration of the ability to potentiate the duration of sleep in phenobarbital-induced sleep, PCE (at 800 mg/kg) produced a close activity (287.6±5.48) to the standard agent, diazepam (302. 1 ±4.83). The ability to protect the animals and/or delay the onset of convulsions to varying degrees may be attributed to the presence of bioactive phytoconstituents present in both plants. The phytochemical analysis revealed that both extracts tested positive to flavonoids, tannins, alkaloids and phlobatanins (Table 1). JCE equally gave a positive reaction for saponins. A positive correlation between the anticonvulsant and sedative activity of chemical constituents isolated from medicinal plants have well been documented (Ali and Chaudhary, 2011; Abdel-Rahman *et al.,* 2015). There are also reports that these constituents act through enhancement of GABA-ergic activity in attenuating seizure and prolonging the duration of sleep (Rang *et al.,* 1999; Li-Ping *et al.,* 2008). Thus, It may be inferred that these constituents are likely responsible for the claimed activity as observed in the present study.

Table1 Preliminary phytochemical analysis of JCE and PCE

Phytochemical	JCE	PCE
Flavonoid	+	+
Tannins	+	+
Saponin	+	-
Reducing sugar	--	
Alkaloids	+	+
Phlobatanins	+	+
Starch	- -	

Key: + = present -= absent

Table 2 Effect of JCE and PCE on pentylenetetrazole (PTZ)-induced convulsion in mice

Treatment	Dose mg/kg	Latency of clonic convulsion(min)	Latency of tonic convulsion (min)	Mortality (within 60 min)	% Protection
Control	-	1.62±0.24	3.67±0.73	5	0
JCE	200	2.02±0.29	5.10±0.39*	5	0
	400	3.24±0.63	9.04±1.25**	5	0
	800	2.02±0.29	5.10±0.39*	5	0
PCE	200	2.54±1.10	4.90±1.99	4	20
	400	3.10±1.40	5.95±2.27*	3	40
	800	6.24±1.82**	30.60±12.16***	2	60
Diazepam	3	60.00±0.0***	60.00±0.0***	0	100

The results are expressed as mean± S.E.M (n=5); *, **, ***indicate significance compared to PTZ-induced seizure control at P <0.05, P<0.01, P<0.001 respectively (Dunnett's multiple comparison test). JCE- *J. curcas* extract, PCE- *P. capitata* extract.

Table 3 Effect of JCE and PCE on isoniazid (INH)-induced convulsion in mice.

Treatment	Dose (mg/kg)	Tonic-clonic seizure onset (min)	Mortality (within 60 min)	% Protection
Control	-	28.84±1.79	5	0
JCE	200	33.46±2.26	5	0
	400	34.88±2.23	4	20
	800	49.92 ±2.07**	3	40
PCE	200	28.80±0.97	5	0
	400	29.80±1.28	5	0
	800	40.60±3.11**	5	0
Diazepam	3	111.8±8.200***	0	100

The results are expressed as mean± S.E.M (n=5); *, **, ***indicate significance compared to INH-induced seizure control at P<0.05, P<0.01, P<0.001 respectively (Dunnett's multiple comparison test). JCE- *J. curcas* extract, PCE- *P. capitata* extract.

Table 4 Effect of JCE and PCE on phenobarbitone-induced sleep

Treatment	Doses (mg/kg)	Onset time of sleep (min)	Duration of sleep(min)
Control	-	36.96±2.34	213.2±4.12
JCE	200	29.80±0.20**	227.4±2.04
	400	26.60±0.66**	239.2±9.15**
	800	13.90±1.20***	283.2±1.62***
PCE	200	34.29±1.02	226.9±5.89
	400	29.98±2.03**	233.1±2.32**
	800	14.90±1.30***	287.6±5.48***
Diazepam	3	8.880±0.59***	302. 1 ±4.83***

The results are expressed as mean± S.E.M (n=5); *, **, ***indicate significance compared to PB-induced sleep control at P<0.05, P<0.01, P<0.001 respectively (Dunnett's multiple comparison test). JCE- *J. curcas* extract, PCE- *P. capitata* extract.

Furthermore, the acute toxicity revealed that *J. curcas* did not produce any obvious signs of toxicity or mortality up to 2900 mg/kg. Therefore, the LD_{50} was estimated to be 3808 mg/kg, which indicate a fairly safe profile. The acute toxicity of *P. capitata,* on the other hand, gave an LD_{50} greater than 5000 mg/kg, an indication of a high safety profile.

4. CONCLUSION

The results of the present study undoubtedly showed that both extract of *J. curcas* and *P. capitata* posses promising anticonvulsant and sedative activity. This supports the evidence for their folkloric usage. Further studies are, however ongoing to isolate and identify the active principles responsible for their anticonvulsant and sedative activity and elucidation of their pharmacological mechanisms.

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Conflict of Interest:
The authors declare that there are no conflicts of interests.

Peer-review:
External peer-review was done through double-blind method.

Data and materials availability:
All data associated with this study are present in the paper.

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